REMARKS

The foregoing amendment incorporates into claim 1 the subject matter of claim 5. Claim 5, now redundant, has been cancelled. In paragraph 1 of the Office Action, the Examiner noted certain errors in some of the claims. These are regretted and they have now all been corrected – without cross-outs or underlines – in the claims shown on pages 2-7. Claims 34-37 have been cancelled and there will be no further mention of said claims in these Remarks.

In addition, the written description has been amended in order to update the status of copending patent applications, to correct typographical errors, and to provide sequence identification where necessary.

Defective Declaration

In Paragraph 2 of the Office Action, the Examiner notes that the Rule 63 Declaration submitted with this application is defective. Accompanying this response is a new Declaration signed by inventors Richard T. Dean and John Lister-James. The third inventor, William McBride, is no longer employed by Diatide, Inc., the Assignee. He has been asked to execute the Declaration and, when this is done, a Declaration executed by all three inventors will be submitted.

Sequence Disclosures

In Paragraph 3 of the Office Action, the Examiner notes that this application does not comply with the amino acid sequence rules.

Documents complying with Rules 821-825 are being transmitted to Mail Stop Sequence.

In addition, amendments to pages 12, 19, 20, 21 and 23 of the specification have been made to insert Sequence Identifications.

The Abstract

In Paragraph 4 of the Office Action, the Examiner has objected to the Abstract of the disclosure because of the presence of the word "said". In response to this objection, Applicants have provided a rewritten Abstract. The new Abstract also deletes extraneous terms such as "this invention relates to".

Objections to the Disclosure

In Paragraph 5 of the Office Action, the Examiner has objected to the disclosure because of certain informalities and misspellings. In the foregoing amendment, the misspellings noted by the Examiner, as well as some others, have been corrected.

The status of all the patent applications referred to on page 7 has been brought up to date by inserting the numbers of issued U.S. Patents. In some instances, the Serial Numbers of applications have been changed. This was done in instances where the originally-noted application has been abandoned and replaced by a divisional or continuation application having the essentially identical disclosure. In each instance, the continuing application has matured into a patent. No new matter has been added.

Rejection of Claims 34-37

In Paragraph 6 of the Office Action, the Examiner has rejected claims 34-37 for failure to comply with the requirements of the first paragraph of 35 U.S.C. § 112. These claims have now been cancelled. As noted above, no further reference will be made to these cancelled claims.

Rejection under 35 U.S.C. § 112

In Paragraph 7 of the Office Action, claims 7, 8 and 17 have been rejected for failure to comply with the requirements of the second paragraph of 35 U.S.C. § 112.

> Claims 7, 8, 17 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claims for the phrase "the radiolabel binding moiety" at claim 7, line 2. Note that independent claim 1, line 4, uses the terminology "radiolabel complexing moiety". Claim 17 is indefinite because it requires "an effective diagnostic amount of the reagent of Claim 2". However, the reagent of claim 2 does not comprise a radiolabel, and accordingly, it is not possible for there to be an effective amount of the unlabeled reagent. There is no antecedent basis in the claims for the phrase "the technetium-99m" at claim 17, line 3, because claim 2, upon which claim 17 depends, does not recite a radiolabeled reagent and does not recite that the reagent is complexed with technetium-99m. At claim 37, last line, the phrase "at least one of" should be inserted after "determining" so that the result of the claimed method is consistent with the preamble of the claim and so that it is clear that determining the existence and determining the locus are in the alternative to one another.

The foregoing amendments to claims 8 and 17 have obviated this ground of rejection.

In claim 7, the term "radiolabel binding moiety" has been changed to "radiolabel complexing moiety", following the language of claim 1.

In claim 17, the dependency has been changed from claim 2 to claim 8, which recites the presence of a radiolabel.

Applicants are presenting a new claim 38, dependent from claim 17 and incorporating the limitations of claim 2.

Objections to Claims 2, 3 and 17

In Paragraph 8 of the Office Action, claims 2, 3 and 17 have been objected to as being in improper dependent form for failure to further limit the subject matter of a previous claim. The foregoing amendment changes the rejected claims and it is submitted that they are now in proper dependent form. Specifically, in claims 2 and 3, the connector has been changed from "is selected from the group consisting of" to "comprises".

With these changes, structure I in claim 2 is now deemed to include the -CO- group attached to (amino acid)[1], and structure II in said claim is now deemed to include the -NH- group attached to (amino acid)[1]. Similar results are obtained by the change of connector in claim 3.

As far as claim 17 is concerned, its change of dependency from claim 2 to claim 8 obviates the Examiner's objection.

Double-Patenting Rejection

In paragraph 9 of the Office Action, claims 1-3, 5-8, 11-17 and 19 have been rejected on the ground of obviousness-type double patenting over the claims U.S. Patent No. 5,849,261.

In order to obviate this ground of rejection, Applicants are submitting a Terminal Disclaimer complying with Rule 321(c).

Effective Filing Date for the Claims of this Application

In Paragraph 10 of the Office Action, the Examiner asserts that the effective filing date for all of the claims of this application is deemed to be 2 May 1994, the filing date of the instant application, rather than the filing date of Application No. 07/807,062. Nevertheless, this application remains a continuation-in-part of the earlier-filed application because it discloses subject matter included in the earlier application. It is also noted that the instant application has been terminally disclaimed over U.S. Patent No. 5,443,815, which matured from the earlier-filed application, thereby indicating that at least some of the claims in this application are not patentably distinct.

The Examiner notes that, on the basis of their priority claims, U.S. Patents Nos. 6,654,272 and 5,849,260 are available prior art under 35 U.S.C. § 102(e). This is essentially correct. The Examiner also pointed out a discrepancy in the priority situation as regards these two patents. The cover page of the '260 patent says that it is a continuation of Application No. 886,752 which, in turn, is a continuation of Application No. 653,012. This is incorrect; Application No. 886,752 is a continuation-in-part of Application No. 653,012. Applicants appreciate the Examiner having called this matter to their attention; it will be corrected in due course.

Rejection over U.S. Patent No. 5,443,815

In Paragraph 12 of the Office Action, the Examiner has rejected claims 1-3, 5-8, 11-17 and 19 under 35 U.S.C. § 102(e) as anticipated by Dean U.S. Patent No. 5,443,815 ("Dean '815").

> Claims 1-3, 5-8, 11-17, 19 and 34-36 are rejected under 35 U.S.C. § 102(e) as being anticipated by Dean et al. (U.S. Patent No. 5,443,815). Dean et al. '815 teaches specific peptides in Table I which comprise a specific binding compound (e.g., the GRGD of SEQ ID NOS:2 and 3 or the RALVDTLK of SEQ ID NO:4) and a radiolabel complexing moiety (e.g., the GGC or SEQ ID NO:2 or the maGGG and PenGGG of SEQ ID NOS:3-4). The peptides are labeled with Tc-99m (see Example 2). More generally, the peptides can be labeled by incubation of the peptide in the presence of a stannous chloride reducing agent, and a kit can be provided for preparing the radiolabeled peptide by a reduction method. See, e.g., column 4, line 45 – column 5, line 5. With respect to claims 11-13, note that process limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. The radiolabeled peptides are used for imaging a mammalian body (see, e.g., the Abstract and column 5, lines 13-43).

This rejection is respectfully traversed, in view of Dr. Richard T. Dean's laboratory notebook pages contained in the attached Appendix A. Applicants will, within the next few days, submit a Declaration verifying the notebook entries.

The patentees of U.S. Patent No. 5,443,815 are Richard T. Dean, William McBride and Scott Buttram. Dr. Dean and Dr. McBride are also inventors in the instant application. The declaration from Dr. Dean will show unequivocally that the subject matter of Dean '815 relied upon by the Examiner was conceived by Dr. Dean. The laboratory notebook pages attached to Dr. Dean's declaration are copies of certain pages of his laboratory notebook identified as "RTD-1", specifically pages 1, 2, 3, 4, 161 and 162. Pages 1 and 2 are dated 11 April 1990 and are headed "Compositions for Modifying the Carboxy Terminus of a Peptide for Labeling with Technetium-99m". The composition identified as No. 1 on page 1 is a reagent comprising a specific binding compound ("peptide") and a radiolabel complexing moiety which is the –GGC of SEQ ID #2 in Dean '815. Page 3 of the notebook is headed "Compositions for Modifying the N-Terminus of Peptides for Labeling with Technetium-99m". Compound No. 2 shows

the radiolabel complexing moiety maGG- of the Dean '815 SEQ ID #3 and #4. This page is also dated 11 April 1990. Radiolabel complexing moieties comprising the GRGD peptide are shown on page 4, under Nos. 4, 5 and 6. The radiolabel complexing moiety PenGG is shown on page 161, which is dated 16 September 1991. This page also shows a specific binding compound comprising a GRGD peptide sequence.

The Declaration of Dr. Dean will be submitted pursuant to Rule 132, as permitted in MPEP §§ 715.01(a) and 716.10 (Feb. 2003). In view of said declaration, the rejection over Dean '815 should be withdrawn.

Rejection over WO 93/10747

In Paragraph 13 of the Office Action, the Examiner rejects claims 1-3, 5-8, 11-17 and 19 under 35 U.S.C. § 102(a) as anticipated by PCT publication WO 93/01747.

> Claims 1-3, 5-8, 11-17, 19, and 34-36 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO Patent Application 93/10747. The WO Patent Application '747 contains the same disclosure as Dean et al. (U.S. Patent No. 5,443,815) applied above, and anticipates the claims for the same reasons set forth above.

As the Examiner correctly notes, WO 93/01747 has the same disclosure as Dean U.S. Patent No. 5,443,815. In view of the forthcoming declaration from Dr. Dean showing that he was the inventor of the subject matter relied upon by the Examiner, this rejection should also be withdrawn.

Rejection over U.S. Patent No. 5,849,260

In Paragraph 14 of the Office Action, claims 1-3, 5-8, 11-17, 19 and 20 have been rejected under 35 U.S.C. § 102(e) as anticipated by Dean U.S. Patent No. 5,849,260 ("Dean '260").

> Claims 1-3, 5-8, 11-17, 19, 20, and 34-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Dean et al. (U.S. Patent No. 5,849,260). Dean et al. '260 teaches specific peptides in the Table at columns 11-12 which comprise a specific binding compound and a radiolabel complexing moiety. The peptides are labeled with Tc-99m, either through use of a stannous chloride reducing agent or through ligand exchange, and kits for preparing the radiolabeled peptides are provided. The peptides are used to image

> thrombus sites in a mammalian body. See, e.g., the Abstract; column 9, lines 14-46; and Example 2. The Table teaches peptides GRGDGGC, maGGRGDF, mmpGGGRGDF, and GRGDGGGGC in which the GGC, maGG, mmpGGG, and GGGC residues, respectively, correspond to Applicants' radiolabel complexing moiety and the remaining residues correspond to Applicants' specific binding compound. Dean et al. '260 also teaches, e.g., the fourth compound of the Table, in which the C-terminal GCamide residues correspond to a peptide comprising 2 amino acids attached to the carbonyl group of Applicants' Z residue, the GGGC residues correspond to Applicants' radiolabel complexing moiety of formula I, and the remainder of the compound corresponds to Applicants' specific binding compound. Note that applicants' claims do not contain any limitations which exclude amino acids containing a thiol group from forming part of, e.g., the specific binding compound, the amino acid or peptide attached to the carbonyl group of Z, or the one or more amino acids which can link the peptide and the moiety.

This rejection is respectfully traversed.

The patentees of Dean '260 are Richard T. Dean and John Lister-James, both of whom are inventors in the instant application. 35 U.S.C. § 102(e), in the version applicable to the instant application, was quoted by the Examiner in paragraph 11 of the Office Action. This section of the patent statute states that "a person shall be entitled to a patent unless the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent. . . ." *(Emphasis supplied).* Since both patentees in the cited reference are also Applicants in the instant application, the reference does not qualify as a patent granted on an application for patent by "another". In these circumstances, the rejection should be withdrawn.

Rejection over U.S. Patent No. 5,561,220

In Paragraph 15 in the Office Action, claims 1, 2, 5-8, 11-17, 19 and 21 have been rejected under 35 U.S.C. §102(e) as anticipated by Dean U.S. Patent No. 5,561,220 ("Dean '220").

> Claims 1, 2, 5-8, 11-17, 19 and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Dean et al. (U.S. Patent No. 5,561,220). Dean et al. '220 teaches specific peptides at column 9, lines 21-30, and in Table I which comprise a specific biding compound and a radiolabel complexing moiety. The peptides are labeled with Tc-99m; ether through use of a stannous chloride reducing agent or through ligand exchange, and kits for preparing the radiolabeled peptides are provided. The peptides are used to image

> inflammation and infection sites in a mammalian body. See, e.g., the Abstract; column 4, lines 41-44; and column 10, lines 4-60. With respect to the peptide, e.g., in Table I, the N-terminal AcKKKKKCG residues correspond a peptide comprising 7 amino acids linked to the amino group of Applicants' Y residue, the CGG residues correspond to Applicants' radiolabel complexing moiety of formula II, and the remaining residues correspond to Applicants' specific binding compound. Note that Applicants' claims do not contain any limitations which exclude amino acids containing a thiol group from forming a part of, e.g., the specific binding compound, the amino acid or peptide attached to the amino group of Y, or the one or more amino acids which can link the peptide and the moiety.

This rejection is respectfully traversed.

In support of the rejection, the Examiner points to the Abstract, to column 4, lines 41-44, to column 10, lines 4-60, and, particularly, to the reagent shown in Table I. The Examiner interprets this reagent as comprising a peptide having the amino acids $AcKKKKKC_{acm}G$-, a radiolabel complexing group of the structure -$C_{acm}GG$-, with the remainder of the reagent being a residue corresponding to Applicants' specific binding compound. Thus, the Examiner's interpretation of this reagent is as follows:

$AcKKKKKC_{acm}$	$C_{acm}GG$	PLYKKIIKKLLES
peptide	chelator	specific binding compound

It is readily apparent that this structural formula would not correspond to structure I of Applicants' claim 1 because, in said formula, it would be the N- terminus rather than the carboxy terminus to which the specific binding compound is attached. Thus, the compound of Dean '220 would, by the Examiner's interpretation, have to correspond to Applicants' structure II. A closer look at the radiolabel complexing moiety of structure II shows that it cannot encompass Dean '220 reagent. In that structure, Y can be cysteine and both $(\text{amino acid})^1$ and $(\text{amino acid})^2$ can be glycines. However, the next amino acid in the Dean '220 reagent is a proline residue. Proline does not have a hydrogen atom attached to nitrogen, and therefore Applicants' -NHR_2 group is not present.

The compound of Table 1 in Dean '220 is the compound disclosed in Dean '220 at column 9, line 30, and is one of ten specifically disclosed compounds at column 9, lines 21-30, and in claim 19. If one follows the Examiner's interpretation of what constitutes a peptide, the radiolabel complexing moiety and the specific binding compound, every one of the disclosed compounds in Dean '220 would have the same specific binding compound beginning with the proline residue next to the second glycine of the radiolabel complexing moiety. Thus, the reference does not disclose any reagents that correspond to Applicants' claims.

(It is noted that the compound shown at column 9, line 26, appears to have the partial structure AcKKC$_{acm}$GC$_{acm}$PLY-, but this is the result of a printing error. In the application as filed – page 14, line 22, and original Claim 20 –, this partial structure is AcKKC$_{acm}$GC$_{acm}$GGPLY-. When the patent was printed, -GG- was omitted. Attached hereto, as Appendix A, are copies of the official filing receipt for Patent Application No. 08/073,577, and pages 1, 2, 14 and 26 of said application. A Certificate of Correction will be requested in due course.)

In fact, the only chelators disclosed in Dean '220 are bisamine bisthiol chelators – see column 10, lines 1-3. Thus, the chelator in all of the specifically disclosed reagents is -CGC-, not -CQA- or -CCG-. Accompanying this response is a declaration from Dr. John Lister-James, one of the inventors, to the effect that, where atomic spacing is such that there can be an –S–N–N–S– chelator or a –N–N–N–S– chelator, technetium would preferably bind to the potential chelator having two sulfur atoms. This declaration is being submitted (as Appendix C) in unsigned form. A signed version will be submitted within the next few days.

For the foregoing reasons, it is believed that this rejection should be withdrawn.

Rejection over WO 93/17719

In Paragraph 16 of the Office Action, claims 1-3, 5-8, 11-17, 19 and 21 have been rejected under 35 USC § 102(a) as anticipated by PCT Publication WO 93/17719.

> Claims 1-3, 5-8, 11-17, 19, 21 and 34-37 are rejected under 35 U.S.C. 102(a) as being anticipated by the WO Patent Application 93/17719. The WO Patent Application '719 teaches specific peptides at pages 20-22 and 24 which comprise a specific binding compound and a radiolabel complexing moiety. The peptides are labeled with Tc-99m, either through use of a dithionate, stannous, or ferrous reducing agent or through ligand exchange, and kits for preparing the radiolabeled peptides are provided (see, e.g., page 14, line 24-15, line 6). The peptides are used to visualize sites in inflammation, including abscesses and sites of occult infection (see, e.g., the Abstract and page 16, lines 9). With respect to the peptide, e.g., at page 20, line 17, of the WO Patent Application '719, the residues $(VGVAPG)_3$ correspond to Applicants' specific binding compound (see also page 12, line &); the residues GGGC correspond to Applicants' radiolabel complexing moiety of formula I; and the residues GCamide correspond to a peptide comprising 2 amino acids lined to the carbonyl group of Applicants' Z.

This rejection is respectfully traversed, particularly in view of the enclosed declaration of Dr. John Lister-James. The Examiner calls Applicants' attention to the specific peptides disclosed on pages 20-22 and 24, which comprise a specific binding compound and a radiolabel complexing moiety. It is true that the peptide reagents disclosed in the reference comprise a specific binding compound and a radiolabel complexing moiety, but none of these compounds fall within the scope of Applicants' claims. The Examiner points specifically to the compound disclosed at page 20, line 17. He characterizes this structure as follows:

VGVAPGVGVAPGVGVAPG	$GGGC_{acm}$	GC_{acm} amide
specific binding compound	radiolabel complexing moiety	2 amino acids

and says that it corresponds to structure I of Applicants' claim 1. This is not a correct interpretation. The radiolabel complexing moiety is not -GGGC- or -GGC-. Rather, it is -CGC-. The Examiner's attention is directed to the Lister-James declaration to the effect

that, when there is a possibility of a chelator being -S-N-N-S- or -N-N-N-S-, technetium preferably binds to the chelator containing two thiol groups. Almost all of the specific peptide reagents disclosed in this reference contain bisamine bisthiol chelators and, even if one can find tripeptide sequences corresponding to Applicants' structure I or II, there is no disclosure in the reference that such tripeptides would function as radiolabel complexing moieties.

Rejection over U.S. Patent No. 6,017,510

In paragraph 17 of the Office Action, claims 1-3, 5-8, 11-17, 19 and 21 have been rejected under 35 U.S.C. § 102(e) as anticipated by Dean U.S. Patent No. 6,017,510 ("Dean '510").

> Claims 1-3, 5-8, 11-17, 19, 21, and 34-37 are rejected under 35 U.S.C. 102(e) as being anticipated by Dean et al. (U.S. Patent No. 6,017,510). Dean et al. '510 is the U.S. equivalent of the WO Patent Application '747 applied above, and anticipates the claims for the same reasons set forth above.

The Examiner apparently made an inadvertent error in asserting that Dean '510 is the equivalent of WO 93/10747. The PCT counterpart to Dean '510 is WO 93/17719, discussed above in connection with the rejection in paragraph 16. WO 93/17719 is actually a continuation-in-part of Dean '510 and it incorporates essentially all of the subject matter of Dean '510. The U.S. equivalent of WO 93/17719 is Dean U.S. Patent No. 5,989,519, which is already of record in this application as a result of the Terminal Disclaimer filed in August of 2001.

For reasons discussed above in connection with the rejection over WO 93/17719, this rejection should also be withdrawn.

Rejection over U.S. Patent No. 5,552,525

In Paragraph 18 of the Office Action, claims 1, 2, 5-8, 11-17, 19 and 21 have been rejected under 35 U.S.C. § 102(e) as anticipated by Dean U.S. Patent No. 5,552,525 (Dean '525).

> Claims 1, 2, 5-8-11-17-19, and 21 are rejected under 35 U.S.C. 102(e) as being anticipated by Dean (U.S. Patent No. 5,552,525). Dean '525 teaches specific peptides in the Table at columns 10-11 which comprise a specific binding compound and a radiolabel complexing moiety. The peptides are labeled with Tc-99m, either through use of a stannous chloride reducing agent or through ligand exchange, and kits for preparing the radiolabeled peptides are provided (see, e.g., column 8, lines 21-65). The peptides are used to visualize sites of inflammation and infection (see, e.g., the Abstract and column 6, lines 52-62). With respect to the peptide, e.g., at claim 20 of Dean '525, the N-terminal residues CG correspond to a peptide comprising 2 amino acids attached to an amino group of Applicants' Y group, the residues CGG correspond to Applicants' radiolabel complexing moiety of formula II, and the remaining residues correspond to Applicants' radiolabel complexing moiety of formula II, and the remaining residues correspond toe Applicants' specific binding compound (see also claim 7 of Dean '525).

The rejection is respectfully traversed.

The sole patentee of Dean '515 is Richard T. Dean, who is an inventor in the instant application. 35 U.S.C. § 102(e), in the version applicable to the instant application, was quoted by the Examiner in paragraph 11 of the Office Action. This section of the Patent Statute states that "a person shall be entitled a patent unless . . . the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent . . ." *(emphasis supplied)*. Since the patentee in the cited reference is also an Applicant in the instant application, the reference does not qualify as a patent granted on an application for patent by "another". In these circumstances, the rejection should be withdrawn.

Rejection over U.S. Patent No. 5,556,609

In Paragraph 19 of the Office Action, claims 1, 2, 5-8, 11-17, 19 and 20 have been rejected under 35 U.S.C § 102(e) as anticipated by Zamora U.S. Patent No. 5,556,609 ("Zamora").

> Claims 1, 2, 5-8-11-17, 19, and 20 are rejected under 35 U.S.C. 102 (e) as being anticipated by Zamora (U.S. Patent No. 5,556,609). Zamora '609 teaches peptides comprising the sequence YIGSR, which targets cells containing receptors for YIGSR such as platelets which occur at thrombosis sites, and also comprising a metal ion-binding domain. See, e.g., the Abstract; column 4, lines 50-64; and column 7, lines 54-63. In Example 7, the metal ion-binding domain is CDG, which corresponds to Applicants' Formula I. In Example 7, the metal ion-binding domains are linked to the YIGSR sequences through one or more amino acids. The peptide in Example 7 labeled with Tc-99m in the presence of a stannous tartrate reducing agent. Labeling kits are also taught (see, e.g., column 7, lines 64-66). With respect to instant claim 13, process steps do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art.

This rejection is respectfully traversed.

With respect to Applicants' reagents, the Examiner points to Example 7 of the references and says that it shows a metal ion binding domain CDG- which corresponds to Applicants' structure II of claim 1 and –GRC which corresponds to Applicants' structure I. (It should be noted that, in SEQ ID NO:3 of Zamora, the formula shown in single-letter version does not correspond to the Formula shown in the 3-letter version. Applicants believe that the single-letter version is correct because this is the only version that has "repeated sequences of YIGSR" as required at column 20, line 65. However, whether the metal ion-binding domain corresponding to Applicants structure I is –GRC or –GDC is not material for purposes of this rejection.) The reagent structure shown in Zamora's Example 7 contains two biological function domains and two metal ion-binding domains (equivalent to Applicants' "radiolabel complexing moieties"). However, Applicants' claims are limited to reagents having <u>one</u> specific binding compound and <u>one</u> radiolabel complexing moiety. Throughout Applicants' disclosure, there are terms such as "<u>a</u> specific binding compound" and "<u>a</u> radiolabel complexing moiety" – see, for example, page 7, line 24, page 8, line 9, page 11, line 2, and claim 1 (an original claim). There is no disclosure in Applicants' specification that the terms "a specific binding compound" and "a radiolabel complexing moiety" can form parts of reagents having two radiolabel complexing moieties as apparently shown in Zamora.

The Examiner's attention is invited specifically to Applicants' listing of peptides at page 12, lines 3-29.

Applicants are aware that – at page 9, lines 15-24 – they have disclosed reagents comprising a polyvalent linking moiety which also contain a plurality of radiolabel complexing moieties. Reagents of this type were the subject of original claims 9 and 10 and also of added claim 24. All of these claims have now been cancelled. Although these claims are no longer in this application, Applicants wish to observe that they would not be anticipated by the Zamora reference.

Inasmuch as Zamora does not teach any reagent included within the scope of Applicant's claims, the rejection under 35 U.S.C. § 102(e) should be withdrawn.

Rejection over WO 89/11877

In Paragraph 20 of the Office Action, the Examiner rejects claims 1, 2, 7, 8, 11-17 under 35 USC §102(b) as being anticipated by PCT Publication WO 89/11877.

> Claims 1, 2, 7, 8, and 11-17 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 89/11877. The WO Patent Application '877 teaches Tc-99m used to radiolabel 2-mercaptoacetate-Gly-Gly-Gly which is attached to a phosphate-containing targeting agent which targets calcified tissues. The radiolabeled compounds are used for detecting the presence or absence of a calcified tissue target site. Radiolabeling can occur in the presence of a reducing agent such as stannous ion, or can be the result of ligand exchange. Kits for radiolabeling are also taught. See, e.g., the Abstract; page 28, line 31 – page 30, line 18; page 34, line 16 – page 35, line 9; and claims 11 and 12.

In order to obviate this ground of rejection, Applicants have incorporated into claim 1 the limitation of claim 5 requiring that the specific binding compound comprise a peptide having from 4 to 100 amino acids. It is noted that claim 5 was not rejected over WO 89/11877.

Rejection over the Morrison et al. Article

In Paragraph 21 of the Office Action, the Examiner rejects claims 1-3, 5 and 19 under 35 USC § 102(b) as anticipated by an article by Christopher A. Morrison, Robert V. Fishleigh, David J. Ward and Barry Robson, "Computer-Aided Design and Physiological Testing of a Luteinising Hormone-Releasing Hormone Analogue for 'Adjuvant-Free' Immunocastration", which was published April, 1987 ("Morrison").

> Claims 1-3, 5, 19, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by the Morrison et al. article (FEBS Letters, Vol. 214, pages 65-70). The Morrison et al. article teaches the LHRH analog LHRH-Gly-Cys-OH, which comprises the C-terminal residues Gly-Gly-Cys. These three C-terminal residues correspond to Applicants' radiolabel complexing moiety of formula I, and the remaining residues correspond to Applicants' specific binding compound which in the case of the Morison et al article binds to the LHRH receptor. See, e.g., page 65.

This rejection is respectfully traversed.

The reference discloses an analogue of LHRH having the structure LHRH-GC-OH Since the amino acid at the carboxy terminus of LHRH is glycine, the Examiner says that the reference teaches a -Gly-Gly-Cys residue and that this tripeptide would correspond to Applicants' radiolabel complexing moiety. The remainder of the LHRH hormone would thus, according to the Examiner, be a "specific binding compound" within the scope of Applicants' claims.

The LHRH analogue is described in the abstract as being "LHRH containing an extension of Gly-Cys at the carboxyl-terminus". There is no teaching that coupling this Gly-Cys extension to LHRH would yield a reagent that would be capable of binding a radionuclide label moiety. And, if even if one would regard -Gly-Gly-Cys as inherently being a radiolabel complexing moiety, we are left with a truncated LHRH – i.e., LHRH without its glycine at the carboxy terminus. There is no teaching anywhere in the reference that this truncated LHRH would retain any of the properties of LHRH. Stated differently, there is no teaching in the reference that the truncated LHRH would be a "specific binding compound" as required in Applicants' claims. The situation with respect to Morrison is similar to that presented in WO 90/10463, discussed below.

For the foregoing reasons, Applicants' claims are not anticipated by the Morrison article.

Rejection over WO 90/10463

In Paragraph 22 of the Office Action, the Examiner has rejected claims 1-3, 5, 6, 19 and 21 under 35 U.S.C. § 102(b) as anticipated by PCT publication WO 90/10463 ("WO '463").

> Claims 1-3, 5, 6, 19, 21 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by the WO Patent Application 90/10463. The WO Patent Application '463 teaches reagents for and a method of imaging inflammation caused by infection. The reagents comprise a labeled recognition agent, where the recognition agent is capable of interacting selectively with activated leukocytes at the inflamed tissue sites. A preferred chelating compound for labeling the recognition agent is a N_3S metal chelating compound. A preferred recognition agent is a chemotactic peptide. The radiolabel can be Tc-99m. Also taught is a peptide recognition agent linked through a Gly_{1-5} spacer to a cysteine residue. Diagnostic kits including instructions for labeling are also taught. See e.g., the Abstract, page 3, lines 7-11, page 4, line 16 – page 5, line 21; page 7, lines 3-9; page 11, line 34 – page 13, line 3; page 26, line 16 – page 27, line 3; page 38, lines 28-35; page 39, line 26 – page 41, line 5, and claims 11, 12, 17, and 29-33.

This rejection is respectfully traversed.

The rejected claims are directed to reagents for imaging a site within a mammalian body, and more particularly for imaging inflammation. Applicants' reagents comprise a specific binding compound ("Labeled Recognition Agent" in the language of WO '463) and a radiolabel complexing moiety ("chelating moiety" in the language of the WO '463). One of the chelating moieties disclosed in the reference is a N_3S chelator compound. (The Examiner states that this is a "preferred" chelating compound, but Applicants have been unable to find any disclosure that N_3S is preferred over other chelating compounds such as N_2S_2, N_2S_3, etc.) However, N_3S metal chelating compounds are disclosed at page 11, line 34, through page 13, line 3.

Applicants have now amended their claims so that their specific binding compound comprises a peptide of between 4 and 100 amino acid residues. WO '463 does not disclose the reagents comprising a specific binding compound ("chemotactic

peptide receptor") and a radiolabel complexing moiety ("chelating moiety"). In Applicants' claims, the distinction between these two functional components of their claimed reagents is carefully maintained. Applicants are claiming a reagent comprising (a) a specific binding compound that includes a peptide of from 4 to 100 amino acids and has the specified molecular weight limitation, which is covalently linked to (b) a radiolabel complexing moiety. The link between (a) and (b) can be – as in claim 6 – through one or more additional amino acids. Furthermore, as noted above in connection with discussion of the Morrison article (paragraph 21 of the Office Action), what WO '463 refers to as a "receptor binding region" must, in order to anticipate Applicants' claims, also function as a "specific binding compound" which, as indicated at page 11, line 11, of Applicants' specification, is a compound that specifically binds to a target site in a mammalian body. The distinction between Applicants' specific binding compound and the radiolabel complexing moiety, which is present in all of Applicants' claims, is not present in the reference.

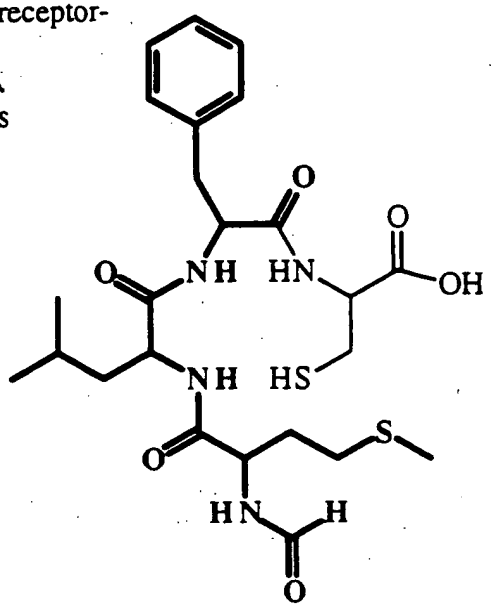
Thus, Example I of the reference can be regarded as teaching radiolabelling of the peptide fMLFC. Although the tripeptide LFC would qualify as a "radiolabel complexing moiety" according to Applicants' definition, the fMLFC peptide of the reference would not comprise both a specific binding compound and a radiolabel complexing moiety. This is illustrated on the following page which shows that the radiolabel complexing region in the reference would have to overlap with the receptor binding region.

It can readily be seen that, if the leucine and phenylalanine residues of the peptides receptor binding region (fMLF-) form part of the chelator, they would be prevented from adopting a conformation capable of binding to a target site with the same high affinity as the unlabelled peptide. In contrast to what is disclosed in WO 90/10463, what Applicants have done is to provide a reagent comprised of a peptide that specifically enables targeting to a site in a mammalian body, said peptide being linked to a separate and distinct radiolabel binding moiety. The reference neither teaches nor recognizes the

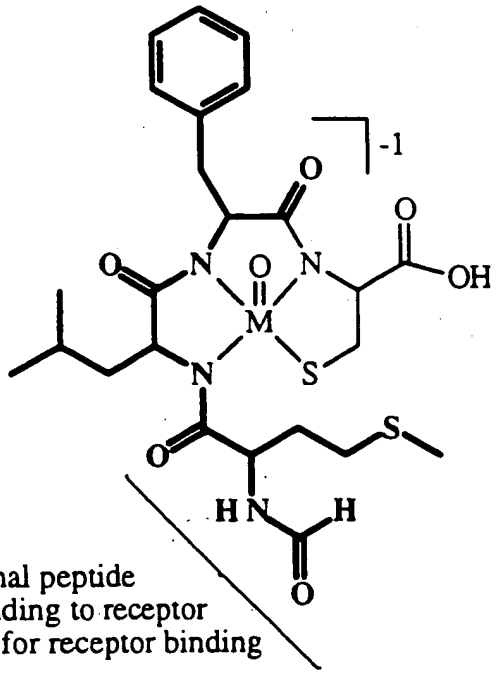
Tc-99m complexing region overlaps receptor-binding region

formyl-Met-Leu-Phe-Cys

Receptor-binding region



(metal M = Tc or Re)



Tc-99m or Re chelate uses amino acids involved in binding region of peptide rendering them unable to assume the conformation needed for receptor binding

Portion of original peptide available for binding to receptor is not sufficient for receptor binding

Bolded structure = specific-binding region

necessity of separating these two functional requirements into structurally distinct components. The Examiner has pointed to a portion of WO '463 – page 38, lines 28-35 – saying that the chemotactic peptide fMLF can be separated from an additional tyrosine, cysteine or lysine residue by a spacer which may comprise from 1 to 5 glycines. However, this does not amount to a disclosure of structurally distinct specific binding compounds and radiolabel complexing moieties. The requirements for an anticipation rejection are that a single reference disclose each and every limitation of the claimed invention. WO 90/10463 does not do this and therefore this rejection should be withdrawn.

Rejection under 35 U.S.C. § 103(a)

In paragraph 23 of the Office Action, the Examiner rejects claims 1, 2, 5-8, 11-17, 19 and 21 as obvious over PCT publication WO 90/10463 ("WO '463") in view of Fritzberg U.S. Patent No. 4,965,392 ("Fritzberg").

> Claims 1, 2, 5-8, 11-17, 19, and 21 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 90/10463 as applied against claims 1-3, 5, 6, 19, 21, and 34 above, and further in view of Fritzberg et al. (U.S. Patent No. 4,965,392). The WO Patent Application '463 does not teach a chemotactic peptide recognition agent labeled with N_3S metal chelating compound which is used to complex Tc-99m. Fritzberg et al. 392 teaches a N_3S metal chelating compound used to label a wide variety of polypeptide and carbohydrate compounds. Fritzberg et al. '392 preferred chelating compound is mercaptoacetylglycylglycylglycine, which is labeled with Tc-99m in the presence of a stannous ion reducing agent. See, e.g., column 6, line 35 – column 7, line 3, column 8, lines 24-29, and Examples I-IIIb, IV, and V. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the mercaptoacetylglycylglycylglycine chelating compound of Fritzberg et al. '392 to label the chemotactic peptide recognition agents of the WO Patent Application '463 because the mercaptoacetylglycylglycylglycine chelating compound of Fritzberg et al. '392 is a species of the N_3S metal chelating compounds generically disclosed by the WO Patent Application '463, because the mercaptoacetylglycylglycylglycine chelating compound of Fritzberg et al. '392 is disclosed as being useful in labeling a wide variety of polypeptide and carbohydrate compounds and therefore would have been expected to be useful in labeling the chemotactic peptide recognition agents of the WO Patent Application '463, because Fritzberg et al. '392 teach that their chelating compounds have the benefit of being able to accurately direct a radionuclide to a preselected site to reduce background radiation, to reduce dosage, to minimize background for in vivo imaging, and to minimize undesirable side effects (see column 1, lines 30-38), and because Fritzberg et al

'392's chelating compound would permit labeling of the WO Patent Application '463's chemotactic peptide recognition agents with Tc-99m, which the WO Patent Application '463 discloses to be a useful radionuclide.

This rejection is respectfully traversed, particularly in view of the foregoing discussion involving the rejection of some of these claims as anticipated by the primary reference.

Applicants have been aware of Fritzberg and, indeed, Fritzberg is disclosed in Applicants' specification at page 5, line 3. The Examiner is correct in his statement that Fritzberg discloses a mercaptoacetylglycylglycylglycine chelating compound (maGGG), but Fritzberg discloses such chelators only for the purpose of labelling proteins. Fritzberg contains no teaching that such chelators can be used for radiolabelling of the chemotactic peptide recognition agents of the type disclosed in WO '463, the primary reference.

In order to support an obviousness rejection which involves a combination of references, there must be a suggestion or motivation for a person skilled in the art to combine the references in order to produce the claimed invention. This motivation is utterly absent in the cited prior art and, therefore, the Examiner's rejection is based on hindsight analysis. The standard under 35 U.S.C. § 103(a) is that Applicants' invention would have been obvious at the time the invention was made. The disclosure of the primary reference is, in pertinent part, limited to chemotactic peptide recognition agents, while Fritzberg is concerned with proteins. In these circumstances, the rejection is not valid and should be withdrawn.

Rejection over the Plank et al. Article

Claims 1-3, 5, 6, 19 and 34 have been rejected under 35 U.S.C. § 102(b) as anticipated by an article by Christian Plank, Kurt Zatloukal, Matt Cotten, Karl Mechtler and Ernst Wagner "Gene Transfer Into Hepatocytes Using Asialoglycoprotein Receptor Mediated Endocytosis Of DNA Complexed With An Artificial Tetra-Antennary Galactose Ligand" which was published in 1992 ("Plank").

> Claims 1-3, 5, 6, 19, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by the plank et al article (Bioconj. Chem., Vol. 3, pages 533-539). The Plank et al article teaches compound 1b (Figure 1), in which the C-terminal Gly-Gly-Cys residues correspond to Applicants' radiolabel complexing moiety of formula I, and the N-terminal glycoside polylysine-Gly residues correspond to Applicants' specific binding compound, and the remaining residues correspond alternatively to portions of Applicants' radiolabel complexing moiety, to Applicants' specific binding compound, or to he amino acids linking the peptide and the moiety. See also the Abstract.

This rejection is respectfully traversed.

In support of this rejection, the Examiner points to compound 1b of the reference and notes that it discloses a C-terminal Gly-Gly-Cys residue.

The instant application is a continuation-in-part of application No. 07/807,062, now U.S. Patent No. 5,443,815. The filing date of the parent application was 27 November 1991, a date earlier than the publication date of Plank. The attention of the Examiner is directed to the amino acid sequence disclosed in the instant application at page 12, line 5, namely GRGDGGC. This sequence is identical to SEQ ID NO:2 of U.S. Patent No. 5,443,815, which is also a C-terminal Gly-Gly-Cys residue. The Examiner notes, in paragraph 10 of the Office Action, that the effective filing date for all of the claims in this application is 2 May 1994, rather than 27 November 1991. However, all that is necessary to antedate a literature reference is a showing that Applicants were in possession at a date prior to the publication date of the reference of that portion of their invention which is disclosed in the reference. This is clearly the situation here and therefore the rejection over Plank should be withdrawn.

Possible Interference with U.S. Patent No. 5,759,516

On 4 May 1999, in the belief that all of the claims in this application contained allowable subject matter, Applicants requested an Interference with U.S. Patent No. 5,759,516 and submitted papers complying with Rules 607 and 608(a). Additional papers were submitted on 26 January 2001.

In paragraph 25 of the Office Action, the Examiner addresses the possibility of an interference with the '516 patent. However, inasmuch as the Examiner has rejected all of the claims in this application, further discussion of a possible interference is premature. This matter can be considered at such time as the Examiner finds that there are allowable claims.

Conclusion

In view of the foregoing amendment, these remarks and the various additional documents being submitted herewith, it is believed that all claims remaining in this application are in condition for allowance. Favorable action is therefore requested.

Respectfully submitted,

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